CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-587

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION (ADDENDUM)

N.D.A.: #20-587

JAN 5 1996

APPLICANT: Bryan

NAME OF DRUG: Talc

INDICATION: Malignant pleural effusion

DOCUMENTS REVIEWED: NDA Volumes 1.1, 1.6, and 1.7; additional publications found by our literature search

MEDICAL OFFICER: Lidya Larson, PharmD
Alison Martin, MD

The unevaluable patients were unevaluable primarily because they died after being randomized but prior to being administered the treatment. However, of the seven patients from the Hamed study who were listed as dying prematurely in the original review (three from the bleomycin group and four from the talc pleurodesis group), only six (three per treatment group) actually died prematurely. The fourth talc patient was unevaluable because of loculations. Thus the table for the Hamed study, which appears on page 4 of the original review, should be replaced by the following table. Each other table is correct with regard to this issue.

5. Hamed et. al., 1989, British Journal of Surgery, 76, 1266-1267, NDA pages 6-022 and 6-041, treated one patient with both treatments (this patient was excluded from the table below). Two patients received bilateral bleomycin pleurodesis. It is, therefore, impossible to reconstruct the data without knowing more about the patients treated twice. The (incomplete) data are:

concurrent (randomized)	died or loculations	recurrence	no recurrence	total
bleomycin	3	2-5*	10-7*	15
talc pleurodesis	4	0	10-1=9*	13
total	7	2-5*	19-16*	29-1=28*

* There were 29 patients enrolled on the study, of which one was treated with both bleomycin and talc pleurodesis. Excluding this patient leaves 28 patients. This patient must have been one of the ten patients who did not recur when taking talc, and thus this number 10 has been decremented by one to nine. It is unclear if this patient recurred or not when taking bleomycin, so it is unclear if the five recurrences should be decremented

to four or if the 10 non-recurrences should be decremented to nine. Furthermore, two patients in the bleomycin group were treated twice each. The intention is to reconstruct patient counts, and not event counts, so each of these patients should contribute one observation only. Again, it is impossible to determine the outcomes of these two patients, so it is unclear if two more should be subtracted from the recurrence count, or two from the non-recurrence count, or one from each. Thus all that can be said with certainty is that there were between two and five patients in the bleomycin group who recurred, and there were between seven and ten patients in the bleomycin group who did not recur.

Vance Berger, Ph.D.
Mathematical Statistician

1/2/96

Concur: Dr. Gnecco
Dr. Chi 1/5/96

CC:

Archival NDA #20-587
HFD-701 / Dr. Anello
HFD-150 / Division File
HFD-150 / Dr. Martin
HFD-150 / Dr. Larson
HFD-150 / Ms. Catterson
HFD-344 / Dr. Lisook
HFD-710 / Dr. Chi
HFD-710 / Mr. Orticke
HFD-710 / Dr. Gnecco
HFD-710 / Dr. Berger
HFD-710 / chron file

CATTELSON

STATISTICAL REVIEW AND EVALUATION

DEC 5 1995

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STATISTICAL ISSUES:

1. It is conceivable that patients were allocated to treatment groups other than randomly. This would certainly constitute a potential bias.

2. In the absense of CRFs, it is impossible to include stratification variables or covariates.

3. Talc is compared to different controls over time. It is possible that these changes in the control group represent improvement in the state-of-the-art treatment of malignant pleural effusions, in which case establishing superiority of talc in the earlier trials would not be overly meaningful. Both talc and controls (all grouped together) will be looked at for possible improvement over time. At least one study (Fentiman, 1986) was reported to have used a sub-optimal dose of the control (500 mg of tetracycline in this case).

4. There was no consistent reporting, across the different studies, of the duration of effusion control, nor was there consistent mention of the number of attempts per patient to achieve control of the symptoms.

5. The terms "control" and "response" varied across the studies, as did the criteria for evaluablity (and in fact some studies did not make these criteria explicit).

6. Different evaluation methods were used across studies, as were different follow-up times, doses of talc, types of talc, routes of administration, and control groups.

7. While random allocation of patients to treatment groups was (presumably) used in most of the studies, random selection of patients from the target population of interest was not. Thus inference is limited to the patients actually enrolled.

1. BACKGROUND

This NDA is based on a literature review only. Talc has been used for years to treat patients with malignant pleural effusions, but talc has never been approved by the FDA for this purpose. It was felt that if approval were granted, then there would be more control over the mechanism by which patients are treated with talc. For example, one concern is the asbestos which some talc contains. Each study was sponsored by an investigator and there was no central body coordinating these research activities. Consequently the studies use different study designs, different doses of talc, different routes of administration, different control groups, different definitions of response, and different lengths of follow-up. No CRFs are available, so it is impossible to determine exactly how the patients were treated and exactly how they responded. The quality of the safety data and prognostic factors for efficacy variables is thus compromised.

Several of the Sponsor's tables are included here for completeness. These are The Sponsor's Tables 8.4.1, Table of Controlled Studies (NDA pages 6-017-6-018); The Sponsor's Table of Follow-up of Patients in Controlled Studies (NDA page 6-060); The Sponsor's Table 8.5.1, Table of Uncontrolled Studies (NDA page 6-063-6-066); The Sponsor's Table of Indications and Sample Sizes (NDA page 6-208); The Sponsor's Table of The Author's Statements about Efficacy of this Treatment (NDA page 6-061); The Sponsor's Table of The Success Rate of Pleurodesis at 30 and 90 Days after Therapy (NDA page 6-216); The Sponsor's Table of Adverse Experiences from Controlled Studies (NDA page 6-059); and The Sponsor's Table of Adverse Experiences from Controlled and Uncontrolled Studies (NDA page 6-233).

This review is organized as follows. In Section 1, the background is given. In Section 2, efficacy data are reconstructed to the extent possible. As there is no gold standard to use as a control group, Section 3 considers time trends to address the issue of different controls. The goal is to determine if the controls were improving over time or not. Likewise, since talc has been administered by different routes at different doses (and, in fact, using different types of talc) across the studies, the same consideration applies to talc.

In Section 4, the efficacy data (which was reconstructed in Section 2) are analyzed by study. The approach taken is to use the Smirnov test statistic as the primary analysis, and to assess significance by using the permutation distribution. Scores tests and a test based on the evaluable subset are presented as secondary analyses. In Section 5 the safety data are considered. Section 6 presents the conclusions based on this review. Section 7 is the statistical appendix, which provides more details on the analysis.

2. DATA RE-CONSTRUCTION AND ANALYSIS STRATEGY:

This section will reconstruct the data to the extent possible given the information available and its limitations. The analysis of this data will be undertaken in the Section 4.

1. Sorensen et. al., 1984, European Journal of Respiratory Distress, 65, 131-135, NDA pages 6-019 and 6-028, gives the following useful data: the patients had malignant pleural effusions secondary to malignancies of the breast, ovaries, or lung. Median response durations were 10 months in each group.

concurrent (randomized)	unevaluable	no response	complete response (pleurodesis)	total
pleural drainage	5	5	7	17
pleural drainage plus sterile talc	5	0	9	14
total	10	5	16	31

2. Boutin et. al., 1985, Review of Malignant Respiratory Distress, 2, 374, NDA pages 6-020 and 6-033, gives the following useful data:

concurrent (randomized)	unevaluable	no response	complete response	total
tetracycline	5	7	8	20
talc poudrage	6	0	14	20
total	11	7	22	40

3. Fentiman et. al., 1983, Cancer, 52, 737-739, NDA pages 6-020 and 6-038, gives the following useful data:

concurrent (randomized)	died	no control	complete control	total
mustine hydrochloride	6	8	9	23
talc British	3	2	18	23
total	9	10	27	46

4. Fentiman et. al., 1986, European Journal of Cancer and Clinical Oncology, 22, 1079-1081, NDA pages 6-021 and 6-035, gives the following useful data:

concurrent (randomized)	died	failed	successful Palliation	total
tetracycline*	2	11	10	23
talc insufflation	6	1	11	18
total	8	12	21	41

* In a letter to the editor (Communications to the Editor, Chest, 102, 6, 12/92, page 1923), Heffner mentions that the tetracycline dose used in this study (500 mg) is known to be sub-optimal.

5. Hamed et. al., 1989, British Journal of Surgery, 76, 1266-1267, NDA pages 6-022 and 6-041, treated one patient with both treatments (this patient was excluded from the table below). Two patients received bilateral bleomycin pleurodesis. It is, therefore, impossible to reconstruct the data without knowing more about the patients treated twice. The (incomplete) data are:

concurrent (randomized)	died	recurrence	no recurrence	total
bleomycin	3	2-5	10-7	15
talc pleurodesis	4	0	9	13
total	7	2-5	19-16	29-1=28

6. Muir et. al., 1987, American Review of Respiratory Disease, 135, A244, NDA pages 6-023 and 6-043, gives the following useful data:

concurrent (randomized)	died	recurrence	no recurrence	total
doxycycline	0	2	13	15
Luzenac talc	0	0	15	15
total	0	2	28	30

No mention is made of the unusually low occurrence of premature death.

7. Hartman et. al., 1992, American Review of Respiratory Disease, 145, 4 Part 2, A868, NDA pages 6-023 and 6-057, used historical controls. The data were given only in percents, with no actual numbers provided:

historical	died	no pleurodesis	pleurodesis	total
bleomycin tetracycline				
talc insufflation				25
total				113

8. Hartman et. al., 1993, Journal of Thoracic Cardiovascular Surgery, 105, 743-748, NDA pages 6-024 and 6-051, used historical controls. The data were flawed by virtue of different evaluability criteria used for the different groups:

historical (30 days, 90 days)	died or unevaluable	no success	success	total
bleomycin tetracycline	16, 7 14, 5	10, 11 18, 19	18, 26 9, 17	44, 44 41, 41
thorascopic talc pleurodesis	6, 18	1, 1	32, 20	39, 39
total	36, 30	29, 31	59, 63	124, 124

9. Adler et. al., Surgery, 1967, 62, 1000-1006, NDA pages 6-025 and 6-044, did not seem to provide any useful data for analysis.

historical	died	no control	control	total
other treatments	0	17	4	21
talc powder aerosol	0	0	4	4
total	0	17	8	25

10. Petrou et. al., Cancer, 1995, 75, 801-805, provided useful safety and efficacy data, but the study was not randomized (talc and shunts were used for different patient populations as explained in the text).

retrospective	died	no response	response	total
shunt	2	1	60	63
insufflated talc	7	1	109	117
total	9	2	169	180

The strategy for the statistical analysis is as follows. Only response data can be reconstructed given the information available. Evaluable patients either respond or do not respond. The majority of the unevaluable patients are unevaluable because they expired prior to actually receiving treatment. Nevertheless, they were randomized (the caveat in item #1 notwithstanding, we assume this, because otherwise no valid analysis is possible). The intent-to-treat approach (Peto, 1987, page 235) would include these patients in a third category, namely death. The three categories can be linearly ordered, since response (taken in some trials to be pleurodesis, complete control of symptoms, no recurrence, or successful palliation) is preferable to non-response, which is in turn preferable to death.

The Smirnov test is the primary analysis, while analyses of secondary importance are based on mean differences utilizing subjective scores. The scores used are 0-0-1 (the test based on proportion responding), 0-1-1 (the test based on the proportion dying prematurely), and 1-2-3 (the equally-spaced scores test). Each of these analyses is performed per the intent-to-treat principle. Another analysis is Fishers exact test based on the evaluable subset. All five analyses are one-sided, and hence for each $\alpha = 0.05/2 = 0.025$. Details of this analytic approach are presented in the statistical appendix.

No analysis is performed on studies known not to be randomized.

3. TIME TRENDS:

We consider the evolution of response rates, both within talc and within controls (regardless of the particular control) over time. Instead of incidence, cumulative incidence is displayed. Thus the last column is always the number of patients treated (100%). The controls data are given below. The Hartman (1992, 1993) data are not presented because historical controls were used for these studies, and it is not known when, in fact, these control patients were treated. The Hamed (1989) data are incomplete, reflecting the incomplete knowledge of the outcomes of all patients. For the purposes of this section, a "concurrent" design is one in which it is known that randomization was not employed, but the patients in both groups were treated at roughly the same time. This applies to the Adler (1967) trial.

Reviewer's Table 1

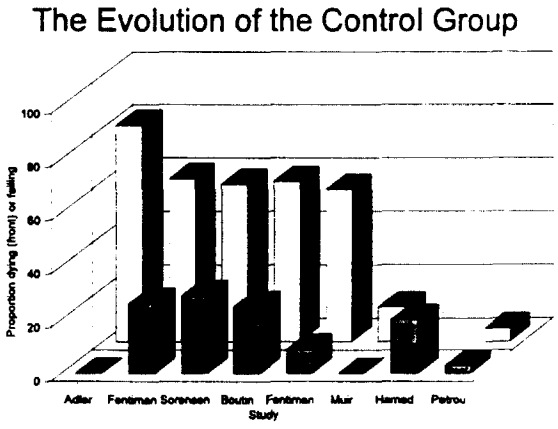
Control Group Time Trends

Investigator	Year	Control	Design	Death Rate	Death or NR	All
Adler	1967	varied	concurrent	0 (0%)	17 (81%)	21 (100%)
Fentiman	1983	mustine	randomized	6 (26%)	14 (61%)	23 (100%)
Sorensen	1984	drainage	randomized	5 (29%)	10 (59%)	17 (100%)
Boutin	1985	tetracycline	randomized	5 (25%)	12 (60%)	20 (100%)
Fentiman	1986	tetracycline	randomized	2 (9%)	13 (57%)	23 (100%)
Muir	1987	doxycycline	randomized	0 (0%)	2 (13%)	15 (100%)
Hamed	1989	bleomycin	randomized	3 (20%)	-	15 (100%)
Hartman	1992	historical	historical	-	-	-
Hartman	1993	historical	historical	-	-	-
Petrou	1995	shunt	retrospective	2 (3%)	3 (5%)	63 (100%)

Reviewer's Figure 1

Control Group Time Trends

This data are graphically displayed in the chart below. Based on the data and the chart, there seems to be a slight time trend. As expected, there is a decreasing trend over time (indexed by investigator along the bottom, or the X-axis) of the proportions not responding (the larger bars in the back) and of the proportions dying prematurely (the smaller bars in the front). This means that the control groups tended to get better over time.



The talc data are given below. Notice that there are separate entries for each of the two analysis times (30 days and 90 days) for the Hartman (1993) study.

Reviewer's Table 2

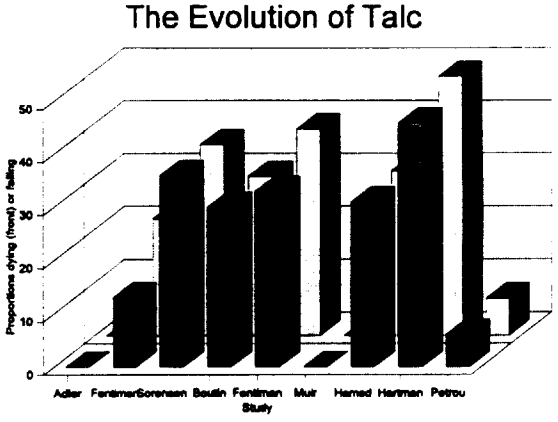
Talc Time Trends

Investigator	Year	Type	Dose	Death	Death or NR	All
Adler	1967	USP	6-8 g	0 (0%)	0 (0%)	4 (100%)
Fentiman	1983	BP	-	3 (13%)	5 (22%)	23 (100%)
Sorensen	1984	-	10 g	5 (36%)	5 (36%)	14 (100%)
Boutin	1985	-	-	6 (30%)	6 (30%)	20 (100%)
Fentiman	1986	-	-	6 (33%)	7 (39%)	18 (100%)
Muir	1987	Luzenac	5 mL	0 (0%)	0 (0%)	15 (100%)
Hamed	1989	-	-	4 (31%)	4 (31%)	13 (100%)
Hartman	1992	-	-	-	-	25 (100%)
Hartman	1993	USP	3-6 g			
30 days				6 (15%)	7 (18%)	39 (100%)
90 days				18 (46%)	19 (49%)	39 (100%)
Petrou	1995			7 (6%)	8 (7%)	117 (100%)

Reviewer's Figure 2

Talc Time Trends

This data are graphically displayed in the chart below. Based on the data and the chart, there does not seem to be a time trend. Had there been one, we would have expected to see a decreasing over time (indexed by investigator along the bottom, or the X-axis) of the proportions not responding (the larger bars in the back) and of the proportions dying prematurely (the smaller bars in the front) to show an improvement. If anything, the proportions seem to be increasing, reflecting a possible worsening of talc over time. This apparent trend may only reflect the unusually high proportions of the Hartman study (using the 90-day data) and the unusually low proportions of the Adler and Fentiman (1983) studies. Of course, the Petrou study goes in the opposite direction.



4. EFFICACY:

The efficacy data are summarized below. Due to potential rounding error, algebraic equalities may appear to be violated. See, for example, the 0-1-1 scores test for the Fentiman (1986) study.

The target population is the set of all patients who ever had malignant pleural effusion or who ever will (or could) have malignant pleural effusions. Since there was no random sampling of patients from this target population, the analyses apply only to the sample at hand, and not to this target population. This is the basis for using permutation tests. Of course, if talc were to be approved, then it would be applied broadly to a general patient population.

There are other limitations as well. For example, there was no consistent reporting of the duration of effusion control, nor was there consistent mention of the number of attempts per patient to achieve control of the symptoms. The terms "control" and "response" varied across the studies, as did the criteria for evaluablity (and in fact some studies did not make these criteria explicit). Different evaluation methods were used across studies, as were different follow-up times, doses of talc, types of talc, routes of administration, and control groups.

Reviewer's Table 3

Intent-to-Treat Analysis

	Intent to Treat Analyses (one-sided, $\alpha = 0.025$)							
	Smirnov*		Scores {0-0-1}		Scores {0-1-1}		Scores {0-1-2}	
Fentiman 1983	control RR	39%	control RR	39%	death	26%	RR Δ	39%
mustine	talc RR	78%	talc RR	78%	death	13%	death rate Δ	13%
	Δ	39%	Δ	39%	Δ	13%	sum Δs	52%
	p	0.0083	p	0.0078	p	0.2296	p	0.0206
Sorensen 1984	control RR	41%	control RR	41%	death	29%	RR Δ	23%
drainage	talc RR	64%	talc RR	64%	death	36%	death rate Δ	-7%
	Δ	23%	Δ	23%	Δ	-7%	sum Δs	16%
	p	0.1924	p	0.1790	p	0.7762	p	0.3784
Boutin 1985	control RR	40%	control RR	40%	death	25%	RR Δ	30%
tetracycline	talc RR	70%	talc RR	70%	death	30%	death rate Δ	-5%
	Δ	30%	Δ	30%	Δ	-5%	sum Δs	25%
	p	0.0621	p	0.0555	p	0.7599	p	0.2360
Fentiman 1986	control RR	43%	control RR	43%	death	9%	RR Δ	18%
tetracycline	talc RR	61%	talc RR	61%	death	33%	death rate Δ	-25%
	Δ	18%	Δ	18%	Δ	-25%	sum Δs	-7%
	p	0.2306	p	0.2104	p	0.9919	p	0.6853
Muir 1987	control RR	87%	control RR	87%	death	0%	RR Δ	13%
doxycycline	talc RR	100%	talc RR	100%	death	0%	death rate Δ	0%
	Δ	13%	Δ	13%	Δ	0%	sum Δs	13%
	p	0.2414	p	0.2414	p	N/A	p	0.2414

* The Smirnov test was the primary analysis.

In each study the talc group showed a higher response rate than the control group did. However, in three of the five studies talc was associated with a higher incidence of premature death than was the control group. It may appear that such premature death is independent of the treatment group to which the patient was randomized, since such death took place prior to the initiation of therapy. This position is not, however, incontrovertible.

For completeness, two of the sponsor's tables are reproduced. These are The Author's Statements about Efficacy of this Treatment (NDA page 6-061) and The Success Rate of Pleurodesis at 30 and 90 Days after Therapy (NDA page 6-216).

Reviewer's Table 4

Analysis of the Evaluable Subset

	Evaluable Subset, Fishers Exact Test (one-sided, $\alpha=0.025$)		
	Success Rate		
	talc	control	
Fentiman 1983	18/20 (90%)	9/17 (53%)	p=0.015
Sorensen 1984	9/9 (100%)	7/12 (58%)	p=0.039
Boutin 1985	14/14 (100%)	8/15 (53%)	p=0.004
Fentiman 1986	11/12 (92%)	10/21 (48%)	p=0.013
Muir 1987	15/15 (100%)	13/15 (87%)	p=0.241

Looking only at the evaluable subset clearly shows talc to be superior to all controls. In the five controlled studies considered, the talc response rate is at least 90% in each, whereas the best control response rate is 87% (Muir), and after that it falls off to 58% (Sorensen). There is a potential bias in the analysis of the evaluable subset in that different numbers of patients in the treatment groups died prior to receiving treatment.

5. SAFETY:

The safety information is contained in the tables on pages 6-059, 6-209, 6-210, and 6-233 of the NDA. The most common adverse experience associated with the use of talc is pain. In fact, all patients receiving talc reported pain to some extent except for the patients on the Fentiman (1983) and the Hartman (1992) studies. The low rates of pain on these studies suggests varying definitions or varying degrees of reporting.

Since the proposed treatment is palliative and not curative, the frequency of pain reported is a concern. On the other hand, pain was also noted by all patients receiving the control in the Sorensen and Hamed studies. The only study in which a clear difference between treatments was found was the Fentiman (1986) study, in which 18 of 18 talc patients reported pain, but only two of 23 tetracycline patients reported pain. The 500 mg dose of tetracycline was reported to be sub-optimal. It is conceivable that more patients would have reported pain had they been dosed with the more aggressive dosage of tetracycline.

The group of patients receiving talc consistently has a higher premature death rate than the group of patients receiving the control. This may or may not be a coincidence. Causes of premature death are given in Table 4 (page 803) of Petrou et. al., Cancer, 1995, 75, 801-805. Some patients had several reasons, but each patient receiving talc who died prematurely had multisystem organ failure listed as the reason or as one of the reasons. Neither of the two patients receiving shunts who died prematurely had this listed as a reason. This may be due to some aspect of the treatment, or it may be due to the fact that the two treatments were administered to different patient populations.

Kennedy et. al., Chest, 1994, 106, 342-346, mentions that fever is a frequent adverse event seen in patients exposed to talc slurry. This paper also mentions respiratory failure as a rare but potentially serious complication. Bouchama et. al., Chest, 86, 5, 11/84, echoed this sentiment. Rinaldo et. al., Journal of Thoracic Cardiovascular Surgery, 85, 523-526, 1983, also mention that talc may predispose patients to respiratory distress syndrome. They suggest talc be used as second-line therapy only, and that when it is used the patients be followed for possible respiratory compromise for 72 hours. Perhaps labelling should reflect this concern. On the other hand, page 6-236 of the NDA mentions that all cases of acute pneumonitis and adult respiratory distress syndrome were associated with talc slurry and has not been associated with insufflation. The pain is attributed to the chest tube, and is said to be no worse than the pain associated with pleurodesis with other agents.

Ladjimi et. al., Review of Malignant Respiratory, 1989, 6, 147-150, provide characteristics of patients for whom talc might be contra-indicated. In particular, the authors find that success may be compromised in patients with

1. Large (over 12 liters) effusions;

2. Pleural involvement with large tumor masses;

3. A very long history;

and

4. Age over 70 years.

In addition, the authors noted better success when the pleural effusions were secondary to broncho-pulmonary cancer than when the pleural effusions were secondary to ovarian cancers. Todd et. al., Chest, 78, 3, 9/80, however, found the least success when the pleural effusions were secondary to breast cancer.

Rodriguez-Panadero and Mejias, American Journal of Respiratory Disease, 1989, 139, 663-667, and Sanchez-Armengol and Rodriguez-Panadero, Chest, 1993, 104, 1482-1485, found low pleural glucose levels and PH to be predictors of poor results from pleurodesis.

One notable aspect of talc's safety profile is that it does not appear to be systemically absorbed. This rules out certain adverse events.

For completeness, two of the sponsor's tables are reproduced here. They are Adverse Experiences from Controlled Studies (NDA page 6-059) and Adverse Experiences from Controlled and Uncontrolled Studies (NDA page 6-233).

6. CONCLUSIONS:

In this reviewer's opinion the evidence presented in this literature-based submission suggests that talc has efficacy. This conclusion is based on the following points.

1. Among evaluable patients, talc has an exceptionally good reported response rate. Page 6-058 lists this proportion as 97% (143/148), but this cannot be confirmed based on the data available. It must be borne in mind, however, that early dropouts due to death from disease could constitute a major source of potential bias, especially because these dropouts occurred with different frequencies in the different treatment groups.

2. In the intent-to-treat population, the talc group consistently has a higher response rate than does the control group. This is based on the Smirnov test.

There are, however, some caveats which need to be considered in the approval decision. These are:

3. There is a much higher incidence of premature death in the talc group than there is in the control group. This is a consistent finding across studies, and it suggests that there may, in fact, be some prosaic explanation. Multisystem organ failure was the predominant cause for premature death in the patients in the talc group in the Petrou study.

4. Pain is almost universal to all talc patients.

5. Other adverse events, such as fever and respiratory failure, were also expressed as a concern by Kennedy and other authors. The NDA mentions that insufflation does not suffer from these drawbacks as the slurry does.

6. Several authors have given conditions under which talc has a lower success rate. This may be important information for labelling.

7. Ruckdeschel (1992) indicates on pages 73 and 74 that tetracycline and bleomycin should be the first-line therapy of choice. Only if they fail should talc be considered. Page 69 also mentions favorably some biologic agents.

Concur: Dr. Gnecco

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This review consists of 17 pages of text, one appendix, eight tables, and one figure.

7. STATISTICAL APPENDIX

This appendix provides more details of the Smirnov test for the response data by illustrating its calculation for the Fentiman (1983) data. If scores (values associated with the outcomes) were provided to the three outcomes, then the score for response, say S(R), would exceed the score for non-response, or S(NR), which would exceed the score for death, or S(D). The choice of these scores is arbitrary subject to the condition that $S(R) > S(NR) > S(D)$. We wish to state that there is a treatment effect in favor of talc when and only when the mean talc score exceeds the mean control score for all possible choices of scores. The technical name for this relationship is stochastic order, and this is equivalent to an ordering on the cumulative distribution functions. Thus we are testing the null hypothesis of no treatment effect against the one-sided alternative hypothesis of stochastic order, as in Case B of Conover (1980, page 369). In this reference the Smirnov test is suggested.

The Smirnov test is more sensitive to stochastic order than any test based on the mean difference of scores. Some scores tests have more power than the Smirnov test to detect superiority of talc with respect to response rate, and other scores tests have more power for detecting superiority of talc with respect to rates of premature deaths, but the Smirnov test is preferable for detecting either eventuality without having to specify which is being looked for. The Smirnov test statistic is, in this case, the larger of two differences between the two treatment groups. The first difference is the proportion of patients who die prematurely, and the second difference is the proportion of patients who respond.

Since patients were not randomly selected from any target population, distributional assumptions cannot be relied upon. Only permutation tests are valid (in the sense that the true rejection probability under the null hypothesis is no larger than the nominal significance level of 0.025). See, for example, Edgington (1995, pages 10-12 and 37-39). We therefore compute the permutation distribution (conditional on the observed margins because these margins are complete and sufficient under the null hypothesis of equality) to assess the significance of each observed result. In the absense of random sampling there is no way to extrapolate from the sample to the population based on statistical arguments alone.

The location of the observed table within the set of possible tables which comprise the permutation distribution (Reviewer's Figure 1) reveals which treatment is preferred (without assessing statistical significance). With fixed margins, only two quantities are varying (there are two degrees of freedom). It is convenient to choose the number of premature deaths in the talc group (S11) and the number of patients in the talc group who either died prematurely or who did not respond (S12) as these two quantities. Reviewer's Figure 1 plots S12 against S11 for each table with the same row and column margins as the observed table. For example, for the observed table $S11=6$ and $S12=6+8=14$. This is noted on the graph by the plus sign at (6,14). The point at which the horizontal and vertical reference lines intersect corresponds to where the two treatment groups show no difference (but this is not a point in the sample space, as it would require 4.5, or 9/2, premature deaths in each treatment group). Four quadrants are created by

these two reference lines. The upper-right quadrant (or either of its borders) is where talc is unequivocally superior to mustine. The lower-left quadrant (or either of its borders) is where talc is unequivocally inferior to mustine. Any other region shows ambiguity. For example, the upper-left quadrant shows superiority of talc with respect to response rate but inferiority of talc with respect to premature death rate.

The boxes on the graph are the rejection region, and the stars are the acceptance region. The 'X's are the randomization region. A method for deciding on rejection or not for each of the points of the randomization region was decided upon prior to unblinding the data (i.e., based on the margins only). Since the observed table fell in the rejection region, it was unnecessary to utilize this procedure. There are 110 points plotted on the graph, corresponding to the 110 possible tables which could have obtained given the margins.

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Peto, R. (1987), "Why Do We Need Systematic Overviews of Randomized Trials", Statistics in Medicine, 6, 233-240.

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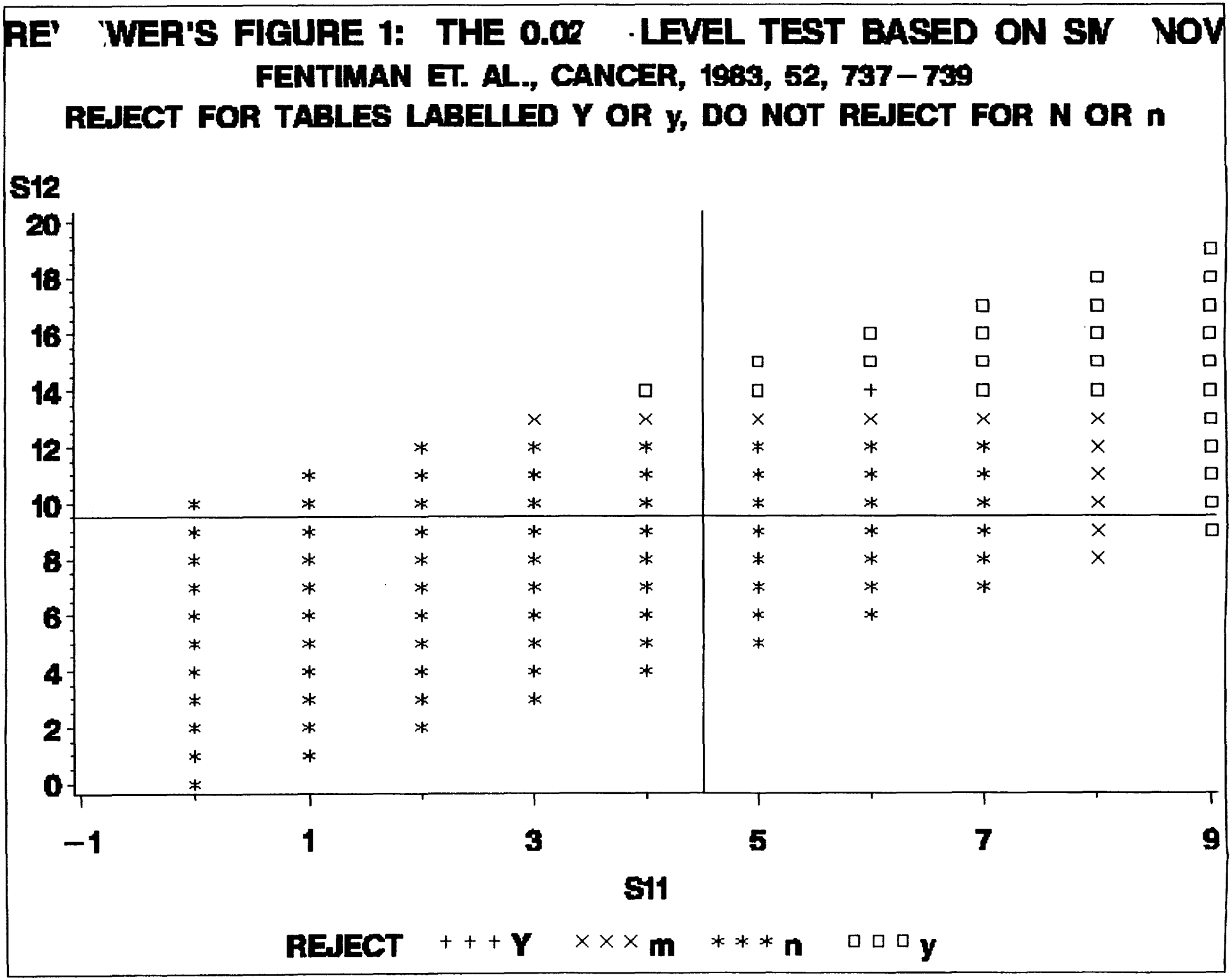
RE' 'WER'S FIGURE 1: THE 0.02 ·LEVEL TEST BASED ON SW NOV
FENTIMAN ET. AL., CANCER, 1983, 52, 737–739
REJECT FOR TABLES LABELLED Y OR y, DO NOT REJECT FOR N OR n
S12
20
18
16
14
12
10
8
6
4
2
0
–1
1
3
5
7
9
S11
REJECT + + + Y × × × m * * * n □ □ □ y

8.4.1 Table of Controlled Studies

Indication 1 - Malignant Pleural Effusion

Investigators, Publication	Completion Status (Starting Date)	Publication Location in NDA	Design	Treatment	Dose	No. of Patients Receiving Treatment (No. of Procedures)	Age Range (Mean)	No. M/F	Duration of Treatment
United States Studies									
Hartman, Gaither, Kesler, Mylet, Brown, Mathur J Thorac Cardiovasc Surg 1993;105:743-8	Complete 1992	Vol. 6, Page 6 051	Prospective, non-randomized, historical controls	Talc insufflation at thoracoscopy	3-6 g	39	41-88 (58.8)	51/49	Single dose
Adler, Rappole Surgery 1967;62:1000-6	Complete (1965)	Vol. 6, Page 6 044	Anecdotal report, historical control	Insufflation of talc powder aerosol via trocar	Not given	4	57-67 (62.75)	50/50	Single dose
Hartman, Mylet, Gaither, Kesler, Mathur Am Rev Respir Dis 1992;145(4 Part 2):A868	Complete (1992)	Vol. 6, Page 6 057	Prospective, non-randomized, historical control	Talc insufflation at thoracoscopy	Not given	25	41-88	Not given	Single dose
Foreign Studies									
Fentiman, Rubens, Haywood Eur J Cancer Clin Oncol 1986;22:1079-81	Complete (1986)	Vol. 6, Page 6 035	Prospective, randomized, active concurrent control	Insufflation of simple talc during thoracoscopy vs instillation of 500 mg Tetracycline in 50 ml. normal saline via chest tube	Not given	18	(50.6)	0/100	Single dose
Hamed, Fentiman, Chaudary, Rubens Br J Surg 1989;76:1266-67	Complete (1989)	Vol. 6, Page 6 041	Prospective, randomized, active concurrent control	Interpleural insufflation of talc at thoracoscopy vs pleural drainage followed by instillation of 1 mg/kg Bleomycin in 50 ml. normal saline via chest tube	Not given	12 (13)	(54.7)	0/100	Single dose

Investigators, *Publication*	Completion *Status* (Starting Date)	Publication *Location in* NDA	Design	Treatment	Dose	No. of Patients Receiving Treatment (No. of Procedures)	Age Range (Mean)	No. M/F	Duration of Treatment
Fentiman, Rubens, Haywood Cancer 1983;52:737-39	Complete (1982)	Vol. 6, Page 6 038	Prospective, randomized, active concurrent control	Insufflation of simple talc at thoracoscopy vs 15 mg mustine hydrochloride	Not given	23	(55.3)	0/100	Single dose
Sorensen, Svendsen, Enk Eur J Respir Dis 1984;65:131-35	Complete (1982)	Vol. 6, Page 6 028	Prospective, randomized, no treatment control	Talc slurry via chest tube	10 g	14	39-79	Not given	Single dose
Boutin, Ray, Villat Rev Mal Resp 1985;2:374	Complete (1985)	Vol. 6, Page 6 033	Prospective, randomized with active concurrent control	Talc or Tetracycline instilled at thorascoscopy; pleural drainage	Not given	40	Not given	Not given	Single dose
Muir, Cerisel, Defouilloy, Broussier et al Am Rev Respir Dis 1987;135:A244	Complete (1987)	Vol. 6, Page 6 043	Prospective, randomized, active concurrent control	Talc insufflation at thoracoscopy vs Doxycycline instillation	5 mL luzenac talc	15 talc, 15 doxycycline	Not given	Not given	Single dose

Follow-up of Patients in Controlled Studies

Author	Follow-Up
Sorensen et al	Chest x-ray performed 1 month after treatment, then every 3 months. Followed until death, average 10 months (range 3-24 months)
Boutin et al	Abstract written 6 months after patients received talc; 6 patients had died, 14 survive with no effusion.
Fentiman et al (1983)	Minimum 6 months; clinical examinations at 4-6 week intervals; chest x-rays at 1 month and thereafter at 3 month intervals compared to baseline.
Fentiman et al (1986)	Minimum: 12 months chest x-rays at 1 month and at later intervals compared to baseline.
Hamed et al	Minimum 1 month; median 24 months. Chest x-ray compared to baseline.
Muir et al	One month minimum; follow-up 4.8 $\pm$ 4.2 months.
Adler & Rappole	Until death, 5-10 months after treatment.
Hartman et al (1993)	Chest x-rays at 30 and 90 days compared to baseline.
Hartman et al (1992)	Thirty and 90 day comparison to baseline.

8.5.1 Table of Uncontrolled Studies

Indication 1 - Malignant Pleural Effusion

Investigators, Publication	Completion Status (Starting Date)	Publication Location in NDA	Design	Treatment	Dose	No. of Patients Receiving Treatment (No. of Procedures)	Age Range (Mean)	No. M/F	Duration of Treatment
United States Studies									
Adler and Sayek Ann Thorac Surg 1976;22(1):8-15	Complete (1970)	Vol. 6, Page 6 089	Anecdotal report	Talc instillation intercostal tube thoracostomy	10 g	41 (44)	17-81	Not reported	Single dose
Aelony, King & Boutin Ann Intern Med 1991;115:778-82	Complete (1983)	Vol. 6, Page 6 096	Prospective evaluation	Talc poudrage/thoracoscopy	5 mL (2.5 g)	41 (42)	35-89 (66.2)	26/15	Single dose
Camishion, Gibbon & Nealon Surg Clinics of NA 1962;42:1521-6	Complete (1960)	Vol. 6, Page 6 101	Anecdotal report	Talc poudrage/thoracotomy	2-3 test tubes	34	30-73 (56 5)	21/13	Single dose
Chambers West J Surg Obstet, Gynecol 1958;66:26	Complete (1952)	Vol. 6, Page 6 107	Anecdotal report	Talc instillation by intercostal intubation	2-4 drams	20	36-73 (55 1)	8/12	Single dose
Colt & Dumon Chest 1994;106(6):1776-80	Complete (not given)	Vol. 6, Page 6 110	Anecdotal report	Thoracoscopic talc insufflation	4 g	12	Not given	Not given	Single dose
Daniel, Tribble & Rodgers Ann Thorac Surg 1990;50:186-9	Complete (May 1982)	Vol. 6, Page 6 115	Anecdotal report	Thoracoscopy and talc insufflation	up to 10.5 g	20	?-78 (N/A)	Not given	Single dose
Factor Arch Pathol 1975;99:499-502	Complete (December, 1971)	Vol. 6, Page 6 119	Anecdotal report	Intrapleural instillation of quinacrine hydrochloride and talc	Not given	1	73 (N/A)	1/0	Single dose
Haupt, Camishion, Templeton & Gibbon JAMA 1960;172:918-21	Complete (12/27/56)	Vol. 6, Page 6 123	Anecdotal report	Talc poudrage	Not given	19	30-72 (56 6)	11/8	Single dose

Investigators, Publication	Completion Status (Starting Date)	Publication Location in NDA	Design	Treatment	Dose	No. of Patients Receiving Treatment (No. of Procedures)	Age Range (Mean)	No. M/F	Duration of Treatment
LoCicero Ann Thorac Surg 1993;56(3):641-3	Complete (prior to January, 1993)	Vol. 6, Page 6 127	Anecdotal report	Talc insufflation with video-assisted thoracoscopy	5 g	40	Not given	Not given	Single dose
Prorok & Nealon Bull Soc Intern Chir 1968;6:630-6	Complete (6/22/61)	Vol. 6, Page 6 130	Anecdotal report	Talc poudrage by limited thoracotomy	Not given	29	31-73 (57 5)	21/8	Single dose
Rinaldo, Owens & Rogers J Thorac Cardiovasc Surg 1983;85:523-6	Complete (prior to May, 1982)	Vol. 6, Page 6 137	Anecdotal report	Intrapleural talc instillation	10 g	3	35-81 (51)	1/2	Single dose
Shedbalkar, Head, Head, Murphy & Mason J Thorac Cardiovasc Surg 1971;61:492-7	Complete (prior to April, 1970)	Vol. 6, Page 6 141	Anecdotal report	Talc pleural symphysis	Not given	28	49-77 (60 6)	15/13	Single dose
Foreign Studies									
Bal & Hasan Int Surg 1993;78(4):324-7	Complete (January, 1984)	Vol. 6, Page 6 147	Anecdotal review	Talc pleurodesis by thoracoscopy	2-5 g	213	41-90 (~65)	91/122	Single dose
Boniface & Guerin Rev Mal Resp 1989;6:133-9	Complete (October, 1980)	Vol. 6. Page 6 151	Retrospective study	Talc instillation with thoracoscopy	5 ml	302	23-93 (64)	162/140	Single dose
Bouchama, Chastre, Gaudichet, Soler & Gilbert Chest 1984;86(5):795-7	Complete (May, 1982)	Vol. 6, Page 6 159	Anecdotal report	Talc pleurodesis under pleuroscopic guidance	2 g	1	40 (N/A)	0/1	Single dose
Canto, Arnau & Moya Res Surg 1991;3/1 46-8	Complete (1979)	Vol. 6. Page 6 162	Anecdotal report	Talc pleurodesis by thoracoscopy	5 g	208	16-88 (57)	Not given	Single dose
Ladjimi, M'Raihi, Djemel, Mathlouti, Ben Ayed & Zegaya Rev Mal Resp 1989;6:147-50	Complete (1983)	Vol. 6. Page 6 165	Anecdotal report	Talc pleurodesis under thoracoscopic control	2-3 cm^3	218	27-75 (49 6)	Not given	Single dose

Investigators, Publication	Completion Status (Starting Date)	Publication Location in NDA	Design	Treatment	Dose	No. of Patients Receiving Treatment (No. of Procedures)	Age Range (Mean)	No. M/F	Duration of Treatment
Ohri, Oswal, Townsend & Fountain Ann Thorac Surg 1992;53:1038-41	Complete (January, 1989)	Vol. 6, Page 6 169	Retrospective review	Talc administration during thoracoscopy	2-5 g	37	55-77 (67.8)	~2/1	Single dose
Pearson & MacGregor J Thorac Cardiovasc Surg 1966;51:732-8	Complete (April, 1961)	Vol. 6, Page 6 173	Anecdotal report	Talc poudrage by various methods	Not given	17 (19)	22-74 (52.1)	5/12	Single dose
Rodriguez-Panadero & Lopez Mejias Am Rev Respir Dis 1989;139(3):663-7	Complete (1982)	Vol. 6, Page 6 180	Prospective study of prognostic factors (pleural glucose and pH levels) in treatment outcome in MPE	Talc pleurodesis	Not given	62	Not given	Not given	Single dose
Sanchez-Armengol & Rodriguez-Panadero Chest 1993;104(5):1482-5	Complete (1982)	Vol. 6, Page 6 185	Cohort analytic prospective study	Talc pleurodesis with thoracoscopy	Not given	125	Not given	Not given	Single dose
Scarbonchi, Boutin, Carnigno & Scarbonchi-Effimief Poumon 1981;37:283-9	Complete (12/31/79)	Vol. 6, Page 6 189	Anecdotal report	Talc poudrage with thoracoscopy	4-5 ml	77	Not given (59.8 MPE pts.)	41/36	Single dose
Todd, Delarue, Ilves, Pearson & Cooper Chest 1980;78:542-3	Complete (prior to September, 1980)	Vol. 6, Page 6 196	Anecdotal report	Talc insufflation by various methods	Not given	178 (197)	Not given	Not given	Single dose
Weissberg Poumon-Coeur 1981;37(5):291-4	Complete (1974)	Vol. 6, Page 6 197	Anecdotal report	Talc insufflation during pleuroscopy or through trocar	2 g max	77	18-82 (not available)	50/27	1 or 2 talc admin

Indication 2 - Pneumothorax

Investigators, Publication	Completion Status (Starting Date)	Publication Location in NDA	Design	Treatment	Dose	No. of Patients Receiving Treatment (No. of Procedures)	Age Range (Mean)	No. M/F	Duration of Treatment
Foreign Studies									
Chappell, Johnson, Wagner, Seal, Berry & Nicholson Br J Dis Chest 1979;73:285-8	Complete (Treatment 1939-1964; evaluation 1979)	Vol. 6, Page 6 201	Retrospective study	Intrapleural poudrage with talc or kaolin	Not given	210	Not given	128/82	Single dose
Lange, Mortensen & Groth Thorax 1988;43:559-61	Complete (Treatment 1951-1963; evaluation 1985)	Vol. 6, Page 6 205	Retrospective study	Talc poudrage and drainage by intercostal tube	Not given	114	87% <41 yrs. at time of treatment	99/15	Single dose

8.5.4 Overall Summary and Evaluation of Data from Uncontrolled Studies

A review of the literature covering the use of talc in the treatment of malignant pleural effusions (MPE) identified 24 articles describing this treatment, primarily anecdotal reports by physicians of their experience in this area.

The total number of patients described in the 24 papers was 1704 (excluding two of three papers written by the same group of physicians to avoid double-counting). These patients underwent 1727 talc instillations. Of these patients/procedures, 1682 were considered evaluable with 1491 judged by the authors to have had a successful outcome (88.6%).

Number of Papers	Indication	Number of Patients (Procedures)
13	Malignant pleural effusions (MPE)	1192 (1214)
3	Chronic or recurrent pleural effusions	62 (63)
3	Pleural effusions due to cancer	54
3	Pleural effusions	301
2	Various, including MPE	129

Note: There are 34 more patients in the table, itemizing patients per indication, than there are in the overall patient total above. Three papers deal with a series of patients (Camishion et al, 15; Haupt et al, 19; and Prorok and Nealon, 63, including the patients in the first two papers). The patients are all listed in the itemization by paper, but the double counting is eliminated in the overall total.

In those papers where the talc used is described, it is said to be pure and asbestos-free (5 papers). Five authors state that they used US Pharmacopeia-grade talc (the specifications would indicate that it is to be asbestos-free). One author used British Pharmacopeia-grade talc. Four papers stated that "talc de Luzenac" was used. In the remaining nine papers, nothing is said about the purity of the talc used.

The dosage of talc used per instillation ranged from 2-10 g. Two authors used 2 g, three used 2.5 g, two used 2-5 g, one used 4 g, two reported using 5 g, one 6-8 g, two 10 g, and one up to 10.5 g. Other measures of dosage were 2-3 cm^3, 2-3 test tubes full of talc, and 2-4 drams (one author each).

Various methods were described for instilling the talc. All twelve papers published in 1989 or later used thoracoscopy. The earliest paper (1958) mentions "intubation". Papers published in the intervening years used thoracotomy and/or intercostal tubes or trochars. Two papers (1981 and 1984) mention pleuroscopy.

The authors' statements about the efficacy of this treatment were as follows:

Author	Efficacy Statement
Sorensen et al	the addition of talc to pleural drainage produced statistically significant improvement
Boutin et al	six months after treatment talc is more efficacious than tetracycline
Fentiman et al (1986)	talc is superior to tetracycline
Fentiman et al (1983)	talc is superior to mustine
Hamed et al	talc is the most effective agent for controlling malignant pleural effusion in patients fit enough for general anesthesia
Muir et al	doxycycline and talc are equally effective
Adler and Rappole	aerosol insufflation of talc effectively prevented further recurrent effusions
Hartman et al (1993)	the safety and efficacy of talc pleurodesis has been demonstrated
Hartman et al (1992)	talc pleurodesis is superior to the use of bleomycin and tetracycline in the control of malignant pleural effusions

8.7 INTEGRATED SUMMARY OF EFFECTIVENESS DATA

8.7.1 Identification of Studies Labelled Adequate and Well Controlled

Bryan Corporation, the sponsor of this NDA, did not perform any clinical trials. The claim of effectiveness for talc in the treatment of malignant pleural effusion (MPE) is based entirely on literature reports. A search of the literature identified nine controlled trials, of which three were in abstract form.

Of the six complete papers, one, Hartman, DL, Gaither, JM, Kesler, KA, Mylet, DM, Brown, JW and Mathur, PN. Comparison of insufflated talc under thoracoscopic guidance with standard tetracycline and bleomycin pleurodesis for control of malignant pleural effusions. Cardiovasc Surg 1993;105:743-8, appears to have been conducted in accordance with Good Clinical Practice (GCP). The patients provided informed consent prior to treatment and Institutional Review Board approval was obtained.

In this paper, thoracoscopic talc pleurodesis in 39 patients was evaluated against documented controls that consisted of 85 patients who had participated in a randomized study with tube thoracostomy drainage followed by either bleomycin or tetracycline sclerosis. Univariate statistical analysis was applied to discrete preoperative and postoperative variables ($\chi 2$ analysis, with continuity correction when appropriate) and to continuous variables (Student's t test) with Statview II software. The results are shown in the following table:

Success Rate of Pleurodesis at 30 and 90 Days After Therapy

Agent/Technique	30 Days	p Value	90 Days	p Value
Talc/Thoracoscopy	97% (32/33)		95% (20/21)	
Bleomycin/Tube	64% (18/28)	0.002	70% (26/37)	0.04
Tetracycline/Tube	33% (9/27)	<0.001	47% (17/36)	<0.001

Number of patients with successful pleurodesis expressed as a percentage and fraction (in parenthesis) of the total number of evaluable patients within treatment groups. *P* values generated by X^2 versus talc.

In the remaining five papers, Sorensen, PG, Svendsen, TL and Enk, B. Treatment of malignant pleural effusions with drainage, with and without instillation of talc. Eur J Respir Dis (DENMARK) 1984;65(2):131-5, mentions that verbal informed consent was obtained but says nothing about approval by an ethics committee. The other four papers make no mention of either informed consent or IRB/ethics committee approval. However, since they have been published in peer-reviewed journals, they may be assumed to have incorporated the elements of GCP in their design and execution, with the possible exception of the Adler and Rappole paper which was published in 1967.

Adverse Experiences from Controlled Studies

Author/ Total No. Pts.	Location in NDA	Adverse Experiences Noted (No. of Pts.)	
		Talc	Control
Sorensen et al n=14 (Talc) n=17 (No Talc)	Vol. 6, Page 6 028	empyema (1); pain (14)	staphylococcal septicemia (1); pain (17)
Fentiman et al (1986) n=18 (Talc) n=23 (Tetracycline)	Vol. 6, Page 6 035	surgical emphysema (2); infection (2); asystolic arrest (2); pain (18)	surgical emphysema (3); brain stem hemorrhage (1); pain (2);
Fentiman et al (1983) n=20 (Talc) n=17 (Mustine)	Vol. 6, Page 6 038	subcutaneous emphysema (1); peroneal nerve palsy (1); post-operative grand mal seizure (1)	subcutaneous emphysema (1); abscess at drain site (1); pulmonary embolus (1)
Hamed et al n=9 (Talc) n=15 (Bleomycin)	Vol. 6, Page 6 041	pain (mild) (9)	pain (mild) (15)
Adler & Rappole n=4 (Talc) n=40 (Historical)	Vol. 6, Page 6 044	pain (mild to moderate) (4); fever (3)	no information available
Hartman et al (1993) n=39 (Talc) n=85 (Historical)	Vol. 6, Page 6 051	discomfort (mild) (38); chest pain (severe) (1); fever (mild) (7); subcutaneous emphysema (mild) (6)	no information available
Hartman et al (1992) n=25 (Talc) n=88 (Historical)	Vol. 6, Page 6 057	pain (severe) (1)	pain (severe) (7)

The criteria for success of the talc insufflation were not specified in the Hartman 1992 abstract. The Boutin abstract speaks of "no more discharge" but does not say how this was determined. Six of the other seven papers describe chest x-rays taken one month after the procedure, showing absence of reaccumulation of fluid. Four of these authors report follow-up beyond one month at three-month intervals for up to one year. The seventh paper (Adler and Rappole) found the pleural space free of fluid upon post-mortem examination 5-10 months following the talc instillation.

Adverse Experiences from Controlled and Uncontrolled Studies

Body System	Adverse Event	COSTART Term	Talc n=1189	Control n=160	Relationship		
					Talc	Procedure	Disease State
Body as a Whole	Pain	PAIN	213[a]	41[1,1,2,4,5]	X	X	X
	Discomfort	PAIN	105[b]		X	X	X
	Chest Pain	PAIN CHEST	1[c]		X	X	X
	Fever	FEVER	223[d]		X		
	Infection	INFECT	9		X	X	
	Empyema	ABSCESS	18		X	X	
	Abscess	ABSCESS	1	1[3]	X	X	
	Cancerous Nodules	CARCINOMA	10				X
	Staphylococcal septicemia	SEPSIS		1[1]	X	X	
	Cellulitis	CELLULITIS	1		X	X	
Cardiovascular	Bleeding	HEM	2			X	
	Myocardial Infarction	INFARCT MYOCARD	3			X	
	Asystolic Arrest	HEART ARREST	2			X	
	Brain stem hemorrhage	INTRACRANIAL HEMORRHAGE		1[2]			X
Nervous	Peroneal Nerve Palsy	PARALYSIS	1			X	
	Grand Mal Siezure	CONVULS GRAND MAL	1			X	
Respiratory	Emphysema (surgical)	EMPHYSEMA	1	4[2,3]		X	
	Emphysema (subcutaneous)	EMPHYSEMA	12[e]			X	
	Pulmonary Edema	LUNG EDEMA	1		X	X	
	Respiratory Failure	APNEA	7		X	X	X
	Pneumonia	PNEUMONIA	7		X	X	X
	Pulmonary Embolism	EMB PULM	2	1[3]	X	X	X
	Adult Respiratory Distress Syndrome	RESPIRAT DIS	3		X	X	
	Acute Pulmonary Distress	RESPIRAT DIS	1		X	X	

[1]No Talc (n=17)
[2]Tetracycline (n=23)
[3]Mustine (n=17)
[4]Bleomycin (n=15)
[5]Historical (n=88)

[a]134 (mild); 4 (mild to moderate); 6 (severe)
[b]38 (mild)
[c]1 (severe)
[d]11 (mild); 2 (severe)
[e]6 (mild); 1 (severe)
[f]15 (mild); 7 (severe)